B3, B4, B5, C1, C2, C3 and C4. Although they were closely related to the strains that have been circulating and associated with outbreaks in the Asia Pacific region since 1997, these strains were not associated with huge outbreak in Peninsular Malaysia. The nucleotides and amino acids substitutions were also analyzed. There was about 18—25% differences in nucleotide sequences between the peninsular isolates and the prototype BrCr-CA-70. Nevertheless, all the changes in VP4 region of the isolated strains were synonymous substitutions.

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**46.015**

**Pharmacological C-Abl Kinase Inhibitors as Potential Anti-Viral Molecules for Dengue Virus**

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*Background:* Dengue virus is a mosquito-borne flavivirus that represents an important emerging infectious disease and is an international health concern. Currently, there is no vaccine or effective antiviral drug to prevent or to treat dengue virus infection. The development of specific anti-dengue molecules would be facilitated by the availability of efficient anti-dengue screening assays, adaptable to high-throughput format. In this study, we have developed an immunofluorescence imaging-based platform that detects dengue virus replication. We used this assay to screen a structurally diverse collection of pharmacological kinase inhibitors.

*Methods & Results:* Small molecule inhibitors of c-Abl and c-Src kinases exhibited significant anti-dengue activity, suggesting that these kinases play critical roles in dengue virus biology. Here, we uncovered a unique role of c-Abl tyrosine kinase harnessed by dengue virus to mediate virus entry via clathrin endocytosis. The infectivity of dengue virus was severely reduced in cells pretreated with GNF2 (specific inhibitor for c-Abl) in a dosage-dependent manner. Moreover, dengue virus infection also triggered the activation of c-Abl by inducing phosphorylation of c-Abl Tyr412. Using immunofluorescence assay and transmission electron microscopy, dengue virus particles were observed binding to the surface of the GNF2 pretreated cells but failed to enter into the cells. These observations were substantiated in cells transfected with small interfering RNA designed to inhibit clathrin and c-Abl expression. Virus infection was significantly reduced in knockdown cells relative to controls cells. Furthermore, dengue virus infection was also aborted in c-Abl −/−, c-Arg −/− and double c-Abl−/−, c-Arg−/− deficient cell line.

*Conclusions:* These findings reveal a novel role for c-Abl in facilitating the clathrin-mediated endocytosis of dengue virus into cells and may serve as a drug target for the development of effective anti-viral strategies against dengue virus infection.

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**Identifying Host Factors Involved in Mediating Vascular Permeability During Dengue Virus Infection**

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*Background:* Dengue virus (DV) is a mosquito-borne virus, belonging to the family Flaviviridae. This virus causes the mild form, Dengue fever (DF) or in severe cases, Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS) characterized by increased capillary permeability. Currently, there is no specific antiviral treatment available to treat patients with DV infection. Furthermore, the pathogenesis of DHF is poorly understood. Hence the aim of this study is to identify the host factors that may play a role in the progression of DHF/DSS during DV infection.

*Methods:* Human Umbilical Vein Endothelial Cells (HUVEC) was infected with DV2 at a multiplicity of infection (M. O. I.) 10. At 72 h post infection (h. p. i.), the expression of different genes specific to endothelial cell biology was analyzed using real-time PCR.

*Results:* Comparing to non-infected controls, host proteins associated with apoptosis such as caspases 1 and 8 were up-regulated in the infected HUVEC. In addition, pro-inflammatory cytokines such as IL-3, IL-7 and IFN- β1 were also up-regulated in the DV-infected cells. These molecules may in turn promote the expression of pro-inflammatory adhesion molecules like ICAM-1, Selectin E and P, as observed in our results. All these cellular molecules are associated with cell migration which could play a role in vascular permeability. In addition, this group of cells also presented with down-regulation of platelet derived factor family genes such as PF4 which may play a role in the aggregation of platelets.

*Conclusion:* Identification of these host proteins allowed us to investigate further their roles in the pathogenesis of DHF/DSS which in turn enable us to identify potential therapeutic leads and better clinical management of patients suffering from/DHF/DSS.

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**46.017**

**B- and T-cell Epitope of the Envelope Glycoprotein E of Dengue Virus Defined by Bioinformatics, ELISA and Enzyme-linked Immunospot**

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*Background:* None of the multivalent dengue vaccines is close to licensure and commercially available even after several decades of dedicated effort. Researchers applied the conventional approaches to vaccine development, which is not successful in all serotypes of dengue virus, thus in our research, we adopted the reverse vaccinology approach to design B- and T-cell epitope based vaccine *in silico* using the genomic and proteomic information. B- and T-cell responses to dengue viruses are of vital importance in both protective immunity and pathogenesis and the peptide vaccine includ-